Grant# DK64539

Center Director: Emeran A. Mayer, M.D.

Center Overview

The Women's Health and Functional Visceral Disorders Center is composed of a cohesive group of clinical investigators and basic scientists with strong independent grant-supported research programs in the interactions between the nervous system and the viscera, with special emphasis on stress neurobiology, sex differences and chronic functional disorders. The main focus of the Center is the identification of sex-related factors that play a role in the development, clinical manifestation and treatment response of two common visceral pain syndromes, e.g. Irritable Bowel Syndrome (IBS) and Interstitial Cystitis (IC). Both disorders are common, occur more commonly in females, appear to show sex differences in treatment responses and cause significant morbidity and impairment in quality of life. The Center has two clinical and two basic science Projects, which closely interdigitate and overlap in terms of thematic, experimental approach and hypotheses. Thus, while the clinical projects study sex differences in central stress circuit activation and peripheral outputs of these circuits in human patients with IBS and IC, the two basic Projects study animal models of both disorders. State of the art technology ranging from molecular biological approaches to functional brain imaging techniques will be used to address the following specific aims in the four Projects:

1. Sex Differences in Central Stress Circuit Responsiveness in IBS and IC patients
2. Sex differences in the colonic responses to stress: Role of CRF pathways
3. Sex differences in neuroendocrine and immunologic responses in IBS
4. Sex differences in CRF, noradrenergic function and oxytocin in cats with IC.

To facilitate the research, the Center has an Administrative Core and a Scientific Core (Neuroendocrine Measures) and will take advantage of existing NIH-funded core and service facilities on campus, including the CURE: Digestive Diseases Research Center, the UCLA Brain Mapping Center and the GCRC.

The Center provides an optimal environment for cooperation and collaboration among its investigators, who already have had a major impact on the field individually. Thus, the synergy expected from the Center promises to have an even larger impact upon expanded research into a highly prevalent, but inadequately treated area of women's health.

Principal Investigator: Emeran A. Mayer, M.D.

Project 1: Sex Differences in Central Stress Circuit Responsiveness in IBS and IC

We hypothesize that altered responsiveness of central stress circuits within the emotional motor system (EMS) can explain many of the cardinal symptoms of Irritable Bowel Syndrome (IBS) as well as other functional visceral disorders such as Interstitial Cystitis (IC). Growing evidence indicates that key components of central stress circuits are sexually dimorphic and differentially responsive in men and women. In particular we hypothesize that female-specific modulators (estrogen, oxytocin systems) of these stress circuits play an important role in the modulation of afferent input from, and efferent output to, the pelvic viscera in patients with IBS and IC. Alterations of brain circuits involving pontine nuclei (locus coeruleus, Barrington's nucleus, parabrachial nucleus, and periaqueductal grey), cortical regions (ventromedial prefrontal cortex, anterior cingulate and insular cortex), and the amygdala complex, may be central to these sex-related differences in pain and stress symptoms. We propose to test specific hypotheses regarding sex-related differences in central stress responses in healthy controls and patients with IBS and IC, using visceral and psychological stress paradigms related to visceral discomfort. Central responses will be examined using (in separate studies) acoustic startle modulation and fMRI. Amygdala complex responsivity will be tested using startle enhancement associated with both viscero-pelvic and non-visceral fear. Differential activation of targeted brain regions to visceral stimulation and anticipation of stimulation will be tested using fMRl. Peripheral and central (from cerebro spinal fluid) concentrations of stress-related neuromodulators including corticotropin releasing factor, norepinephrine and oxytocin will be assessed for gender and illness group interactions and as correlates of the functional measures. These studies will address three specific aims: 1) Are there sex-related differences in central stress and attention responses in healthy controls and/or IBS/IC patients? 2) Are there sex-related alterations in EMS activation in response to psychological or visceral stressors? and 3) Are there alterations in central stress neurotransmitters/modulators consistent with enhanced EMS network activation in women with IBS/IC?

Principal Investigator: Yvette F. Tache, Ph.D.

Project 2: Sex differences in the colonic responses to stress: Role of CRF pathways

Stress is implicated as the causative or complicating factor of symptoms of several diseases including altered bowel habits and visceral hyperalgesia in Irritable Bowel Syndrome (IBS) patients. Our previous work as well as other studies show that the activation of corticotropin-releasing factor (CRF) receptors mediates various stressors-induced alterations of gut motor function and that CRF_1 receptor is mostly involved in the colonic response. Recent evidence also suggests a role of this pathway in stress-related colonic hypersensitivity to colorectal distention. Despite the greater prevalence of stress-related IBS symptoms in women, most of the experimental knowledge of the effects and mechanisms of stress on gut motor alterations and visceral hyperalgesia derives from studies performed in male rodents. The overall goal of the proposal is to characterize the neuroanatomical and biochemical substrata underlying for sex-related differences in stress-induced colonic responses (motility and visceral pain) in rats. Based on presence of estrogen responsive elements on the CRF gene and its modulation by estrogen in the hypothalamus, we will test the hypothesis that estrogen-induced modulation of CRF signaling pathways contributes to the enhanced colonic responses of female rodents to stress. In the specific aim 1, we will build on our data preliminary data and characterizes sex-related differences in stress-induced colonic motor activation and visceral hyperalgesia using psychological and visceral stressors in model of IBS. We will assess with the newly developed CRF_1 and CRF_2 selective receptor antagonists the role of activation of CRF receptors in stress-related colonic responses in female rats and modulation by sex hormones. In specific aim 2, we will define the sex-related differential activation of brain, spinal and enteric circuitry induced by stress, particularly at neuronal sites involved in autonomic and pain modulation and known to express estrogen receptors using Fos expression as a marker of neuronal activation. Double labeling will be used to identify the presence of estrogen receptors and identified CRF and/or oxytocin and noradrenergic neurons. Specific Aim 3 will determine the modulation of CRF and CRF_1 gene transcription by estrogen at specific sites involved in the colonic responses to stress. The regulation of rat and human CRF and CRF_1 receptor promoter activity by estrogens will be further investigated in naive and transfected cells. These studies using functional, neuroanatomical, neurochemical and molecular approaches in rodent model will provide new insight on the interactions between estrogens and CRF pathways as it relates to the visceral response to stress and the underlying mechanisms at the levels of gene regulation and will have relevance to the pathophysiology of stress-related exacerbation of IBS.

Principal Investigator: Lin Chang, M.D.

Project 3: Sex differences in neuroendocrine and immunologic responses in IBS

Studies support a prominent role of stress in irritable bowel syndrome (IBS). The principal branches of the general stress response are the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). The overall hypothesis of this Project is that females and males differ in their HPA axis responsiveness and SNS activation, particularly under stress conditions, and that these differences will help explain the greater vulnerability of females to develop chronic stress-related conditions such as IBS. Furthermore, these sex-related differences in the HPA and SNS are reflected in differences in colonic mucosal immune modulation which in turn relates to the higher prevalence of colonic visceral hypersensitivity in female IBS patients. We will study four subject groups: female IBS patients, male IBS patients, female controls and male controls. In Aim 1, we will test the hypothesis that under basal conditions, males have greater HPA (ACTH, cortisol) and general SNS (cardiosympathetic and sympathoadrenal) activity but females may have greater SNS activity to the pelvic organs. Specifically, we will compare HPA responsiveness in males and females using HPA axis challenge tests, biomathematical modeling analysis to characterize the diurnal rhythm of ACTH and cortisol, and estimate chronically enhanced SNS output to the colon by measuring tissue NE levels and alpha 2-receptor density in colonic biopsies. In Aim 2, we will test the hypothesis that under stress conditions, males show greater general measures of plasma HPA (ACTH, cortisol) and SNS activity (cardio-sympathetic, catecholamines and skin conductance) responses to a visceral stressor (flexible sigmoidoscopy) and a psychological stressor (Trier social stress test) compared to females. In Aim 3, we: will test the hypothesis that symptomatic IBS patients have: altered plasma and mucosal cytokine production which differ in females and males and are related to sex-related differences in visceral pain perception. We will measure plasma and colonic mucosal cytokine markers, and perceptual responses to rectal balloon distension to determine if visceral sensitivity is associated with mucosal and plasma immune markers. The combination of experimental approaches should improve our understanding of the sex-related differences in stress response mechanisms underlying functional pain syndromes.

Principal Investigator: C.A. Buffington, M.D.

P4: Sex differences in CRF, noradrenergic function and oxytocin in cats with IC

The long-term goal is to exploit a naturally occurring bladder disease in domestic cats (Feline Interstitial Cystitis - FIC) to gain a better understanding of a painful bladder disorder in humans called interstitial cystitis (IC), and by extension other pelvic pain syndromes. This is because many patients with IC also have IBS and other neurovisceral disorders that predominantly affect women, and appear to be exacerbated by stress. The studies proposed here are designed to further investigate the causes of these neurological alterations in controlled studies of cats diagnosed with IC and healthy cats. The studies are needed to elucidate the significance of the underlying neurological abnormalities present in human patients with IC. They also are intended to guide the choice of subsequent studies toward the primary systems involved in IC, with the eventual goal of identifying rational treatments of IC in human beings. The overall objective of this proposal is to test the hypothesis that interactions between CRF, sex hormones and the alpha-2 adrenoceptor (α2-AR) play a role in the sex difference in stress-responsiveness of cats with FIC. The rationale for the proposal is based on 1) clinical evidence that females are more prone to develop IC than males (intact males in cats), 2) the gap in knowledge in factors that may account for such sex differences due to the paucity of experimental data in this field, 3) evidence from our recent studies pointing to a role of α2-AR dysfunction in cats with IC, and 4) existing evidence that urothelial and α2-AR function can be modulated by testosterone, estrogen, and oxytocin. By studying a natural occurring animal model of IC which shares many features with a rat model of IBS, and with the respective human patient populations, we will be able to assess the role of sex hormones on the expression of these diseases.

Principal Investigator: Gordon V. Ohning, M.D., Ph.D.

CORE: Neuroendocrine Measures

The Neuroendocrine Assay Core will provide the UCLA Women's Health and Functional Visceral Disorders Center with state of the art resources and expertise related to the measurement of neuroendocrine mediators involved in central and peripheral signaling pathways and interpretation of results. The Core will have the capability to perform radioimmunoassay, HPLC, and MDLC measurement of serum and CSF levels of neuroendocrine mediators in samples obtained from human and animal subjects. The Neuroendocrine Assay Core will be directed by Dr. Gordon V. Ohning, MD, PhD and co-directed by Dr. Joseph Reeve, Jr., Ph.D. The Core will utilize much of the existing equipment and resources that are available in the NIH-funded CURE: Digestive Diseases Research Center/ Antibody and Radioimmunoassay Core (G. Ohning, P.I.) and Peptide Biochemistry and Molecular Probes Core laboratories (J. Reeve, P.I.). Dr. Ohning has formal training in Internal Medicine, Gastroenterology and in the Postdoctoral Research Training Program in Psychiatry and Biobehavioral Sciences. He has considerable experience in radioimmunoassay techniques and ELISA measurements. He has also had a longstanding clinical research interest in functional GI disorders and has collaborated with the P.I. in this area. Dr. Reeve has over 25 years of experience in protein chemistry and purification techniques and expertise in HPLC and Multi-Dimensional Liquid Chromatography (MDLC). He has considerable research experience in isolation, purification, and identification of bioactive peptides and non-peptide transmitters. Peter Chew, M.S. will be the primary technician responsible for the RIA, HPLC, and MDLC techniques required to perform the assays within the scope of the Core services. He has over 25 years of experience with these techniques and will coordinate efforts with the Core Co-Directors and Investigators utilizing the Core Services, including quality control of all procedures and development of new methods for assay. The Director, Co-Director and Primary Technician will work together as a team to provide a cohesive and efficient Core that will not only provide analysis of neuroendocrine samples, but also provide consultation on the correct methods for obtaining and processing samples and the interpretation of results. The Core Laboratory will also provide training as part of the Career Development Program, and participate at all levels in Center operations.